Letter to the Editor

High eosinophil count: A potential biomarker for assessing successful omalizumab treatment effects

To the Editor:

Some patients with atopic asthma have ongoing symptoms and exacerbations despite normal lung function.[1] Poor asthma control, or an exacerbation, often results in the need for intervention with oral corticosteroids.[2] Many factors contribute to the loss of control including allergen exposure and/or a respiratory infection.[3] Because IgE plays an important role in asthma, treatment to reduce serum IgE, and hence tissue-bound IgE, has been shown to modify the response to inhaled allergen and exacerbations.[4,5] Omalizumab (Xolair; Genentech Inc, South San Francisco, Calif), an injectable recombinant humanized mAb that selectively binds to free IgE, is currently indicated in the United States for the treatment of patients (aged ≥12 years) with moderate-to-severe allergic asthma who remain inadequately controlled on inhaled corticosteroids (ICS).[6]

Here we report the findings of a 24-week, multicenter, parallel-group, double-blind, randomized, placebo-controlled trial conducted to fulfill a postmarketing commitment that evaluated the effectiveness of omalizumab in patients aged 12 to 75 years with atopic asthma (elevated serum total IgE levels ≥30-≤1300 IU/mL) who remained symptomatic and uncontrolled on ICS with or without other controller medications despite having normal lung function (baseline predicted FEV_1 ≥80%). The primary end point was the average rate of asthma exacerbations, predefined in the study protocol as a worsening of asthma requiring treatment with oral or intravenous corticosteroids and/or a doubling of the baseline ICS dose for 3 or more days during the treatment period. Further details of study methodology, including secondary and preplanned analyses, are detailed in this article's Online Repository at www.jacionline.org. To investigate what factors might predict treatment outcomes in this patient population, a preplanned analysis was performed in 2 subgroups divided according to eosinophil counts at screening: low (<300/μL) and high (≥300/μL).

Overall, 328 randomized patients received at least 1 dose of study treatment and were evaluable for efficacy and safety (omalizumab [n = 157] or placebo [n = 171]; see Fig E1 in this article's Online Repository at www.jacionline.org). Patient demographics and baseline characteristics were well balanced between the 2 treatment groups, as well as in the subgroups with high (≥300/μL) or low (<300/μL) eosinophil counts at baseline (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org).

The primary end point of the study was not met. Although there was a 27% reduction in protocol-defined exacerbation rates with omalizumab versus placebo (0.21 vs 0.26 per patient during the 24-week treatment period; relative risk [RR], 0.73; 95% CI, 0.44-1.24), this treatment effect was not statistically significant (Table I). A sensitivity analysis showed that the rate of exacerbations defined according to the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) update[7] was reduced by 14% (0.19 vs 0.20; RR, 0.86; 95% CI, 0.48-1.55). In addition, a subgroup analysis demonstrated that there was no information contributed by patients with no prior exacerbations. Because of the fact that patient eligibility for enrollment was highly limited, the study was underpowered to demonstrate a statistically significant treatment effect in the primary end point. As the primary efficacy end point did not reach statistical significance, the improvements in lung function (secondary efficacy end points) observed with omalizumab were not considered statistically significant because of the prespecified gatekeeping strategy used to control the familywise type I error rate (see Figs E2-E4 and Table E3 this article's Online Repository at www.jacionline.org for results of secondary end points/preplanned analyses). Similarly, results for the following subgroup analysis should be interpreted with caution.

It is clinically noteworthy that the treatment response to omalizumab appeared to differ according to patients' blood eosinophil count at baseline. In patients with an eosinophil count of 300/μL or more, omalizumab treatment resulted in a 59% reduction in the rate of protocol-defined exacerbations versus

TABLE I. Change in protocol-defined asthma exacerbation rate over the 24-week treatment period (mITT population), and by high and low eosinophil counts at screening

mITT population	Omalizumab (n = 157)	Placebo (n = 171)
No. of protocol-defined asthma exacerbations, n (%)		
0	133 (84.7)	138 (80.7)
1	21 (13.4)	25 (14.6)
≥2	3 (1.9)	8 (4.7)
Unadjusted exacerbation rate*	0.21	0.26
Poisson regression†		
Ratio of exacerbation rates‡ (95% CI)	0.73 (0.44-1.24)	
P value	.25	
Eosinophil counts at screening	**Omalizumab (n = 51)**	**Placebo (n = 40)**
High		
No. of protocol-defined asthma exacerbations, n (%)		
0	41 (80.4)	25 (62.5)
1	9 (17.6)	9 (22.5)
≥2	1 (2.0)	6 (15.0)
Unadjusted exacerbation rate*	0.25	0.59
Poisson regression§		
Ratio of exacerbation rates‡ (95% CI)	0.41 (0.20-0.82)	
P value	.0125	
Low	**(n = 56)**	**(n = 70)**
No. of protocol-defined asthma exacerbations, n (%)		
0	48 (85.7)	60 (85.7)
1	7 (12.5)	9 (12.9)
≥2	1 (1.8)	1 (1.4)
Unadjusted exacerbation rate*	0.17	0.16
Poisson regression‡		
Ratio of exacerbation rates§ (95% CI)	1.07 (0.45-2.53)	
P value	.8807	

mITT, Modified intent-to-treat population.
*Number of protocol-defined asthma exacerbations/total patient-treatment period.
†Poisson regression with overdispersion model is adjusted for dosing regimen and prior exacerbation status.
‡Omalizumab/placebo.
§Poisson regression with overdispersion model including terms for treatment, dosing regimen, and prior exacerbation status.

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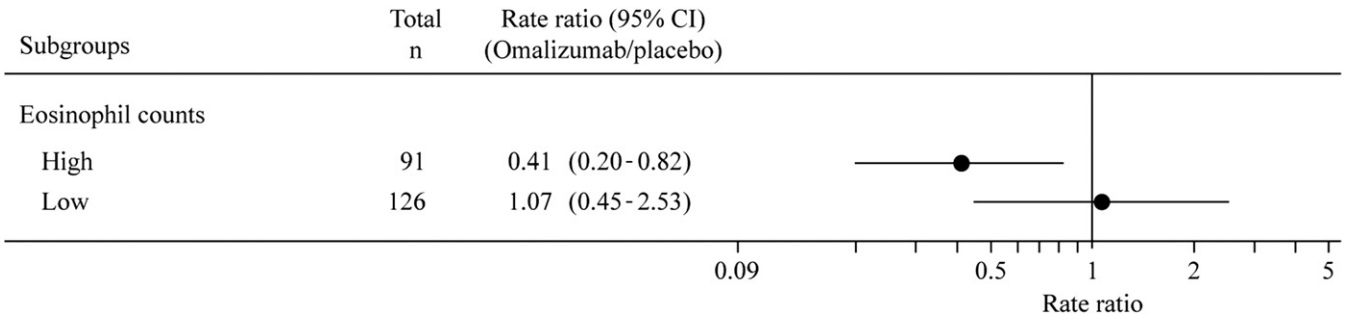

FIG 1. Rate ratio (95% CI) of protocol-defined asthma exacerbation by subgroup.

placebo (0.25 vs 0.59; RR, 0.41; 95% CI, 0.20-0.82; Fig 1). In the corresponding sensitivity analysis according to the ATS/ERS exacerbation definition, the omalizumab group exhibited a 45% reduction compared with placebo (0.22 vs 0.40 per patient; RR, 0.55; 95% CI, 0.25-1.22). In patients with low eosinophil counts at baseline, omalizumab showed no improvement versus placebo in the protocol-defined exacerbation rate (0.17 vs 0.16; RR, 1.07; 95% CI, 0.45-2.53) (Table I).

Although the primary end point was not achieved in this study, the markedly improved effectiveness of omalizumab in terms of the reduction in the rate of exacerbations in the subgroup with high eosinophil count is a potentially important finding. Although the treatment effect was reduced when the ATS/ERS exacerbation definition was used, there remained a trend toward a lower exacerbation rate in omalizumab-treated patients with high eosinophil counts compared with placebo. Furthermore, patients in the placebo group with eosinophil counts of 300/μL or more had a higher exacerbation rate compared with those in the low eosinophil subgroup, suggesting that high eosinophil counts may be a prognostic indicator for patients at greater risk of exacerbations.

Our subgroup analyses therefore indicate that eosinophil count may have value as a biomarker to identify patients with symptomatic asthma despite normal lung function who could potentially benefit from omalizumab treatment. The peripheral blood eosinophil count is a well-recognized marker of inflammation in asthma,[8] and previous studies have demonstrated a consistent pattern of improved clinical outcomes associated with decreased eosinophil counts in patients receiving omalizumab.[9] Eosinophil count is recommended as a supplemental biomarker measure by the Asthma Outcomes workshop.[10]

Omalizumab was well tolerated in the present study, and safety data were consistent with the established profile of omalizumab, with no new safety signals observed. Details of the safety findings are included in Table E4 the Online Repository at www.jacionline.org.

In summary, our findings suggest that the small subpopulation of patients with normal lung function but ongoing symptoms, despite treatment with ICS, who have high peripheral blood eosinophils may benefit from treatment with omalizumab. Although the present study is limited by the lack of statistical significance for the primary end point, the subgroup analyses indicate that eosinophil count may have potential as a biomarker to predict omalizumab treatment outcomes, and should be further investigated in randomized, double-blind, placebo-controlled trials.

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METHODS

Patients

To be eligible for inclusion, patients were required to have inadequate symptom control, defined as a daytime asthma symptom score of 1 or more on at least 20 days and a mean symptom score of 1.5 or more, or nighttime awakening due to asthma symptoms more than 4 times during the 4-week run-in period.

Patients were excluded if they had received chronic systemic corticosteroids (oral or intravenous) within 3 months or had received a burst of oral corticosteroids within 2 weeks prior to screening; had received omalizumab therapy at any time within 12 months prior to screening; had a significant medical illness/active lung disease other than asthma; were pregnant/lactating; or had taken immunosuppressants or other investigational drugs within the 30 days prior to screening.

To increase the rate of enrollment, the study protocol was amended to remove the inclusion criterion requiring that patients had to have had at least 1 exacerbation requiring corticosteroids/a doubling of the dose of ICS.

Study design

After a 4-week run-in period, eligible patients were randomized to receive omalizumab or placebo in a 1:1 ratio for 24 weeks, stratified by study center and dosing regimen (every 2 or 4 weeks). Omalizumab dose was determined on the basis of pretreatment serum total IgE level (IU/mL) and body weight (kg) according to the European omalizumab dosing table, which ensured a minimum omalizumab dose of 0.008 mg/kg/IgE (IU/mL) every 2 weeks or a minimum of 0.016 mg/kg/IgE (IU/mL) every 4 weeks. No modifications to the doses of omalizumab or concomitant asthma/nonasthma medications (established prior to the 4-week run-in period) were allowed during the study.

The study was conducted according to US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guideline for Good Clinical Practice, and any national requirements, and was approved by local or central institutional review boards. Written informed consent was obtained from all patients (or the patients' parent/legal guardian if the patients were younger than 18 years) prior to enrollment.

Randomization and blinding. A permuted block design of randomization was used to ensure treatment balance overall, within each study center, and within the study drug dosing regimens (subcutaneous administration every 2 or 4 weeks). A list of randomization numbers in 10 blocks of 4 was generated for each study center and each of the 2 study drug dosing regimens. A randomization schedule was generated for all sites as an ASCII file by including the following information: randomization number, treatment assignment, site, and dosing frequency. All patients, investigators, site personnel, and the study sponsor were blinded to the treatment assignment throughout the study. Study drug supplies were shipped blinded to treatment assignment to each site. Because of differences in viscosity between the omalizumab and placebo preparations, which may have compromised blinding, the drug was reconstituted and/or administered by an unblinded pharmacist or other designated individual who was not involved in recording study data.

Assessments and variables

The primary efficacy outcome was the average rate of asthma exacerbations during the 24-week treatment period, which started from the first dosing date and ended 30 days following the last dosing date/date of study completion or early discontinuation, whichever was earlier. The definition of asthma exacerbations used in this study predates that specified by a recent ATS/ERS workshop.[E1] A sensitivity analysis was conducted to evaluate the effect of omalizumab on ATS/ERS-defined exacerbations, which excluded doubling of the patient's baseline ICS dose from the protocol definition of an exacerbation.

Secondary outcome measures included change from baseline to week 24 in nocturnal and daytime asthma symptom scores (mean symptom score recorded daily on a 0-4 scale during the last 28 days), and relative change from baseline to week 24 in % predicted FEV_1. Patients monitored their asthma symptoms, peak expiratory flow rate, and rescue medication use by using case report forms provided by the study sponsor, which were completed twice-daily during the 4-week run-in period and the treatment period. All spirometry measurements were performed in accordance with ATS guidelines.[E2]

Safety was evaluated by recording and monitoring the frequency and severity of adverse events (AEs), with particular attention given to AEs of special interest (including malignancies, urticaria, hypersensitivity reaction, injection-site reaction, bleeding-related events, and arterial thromboembolic event). The frequency of serious AEs (including deaths) was also recorded, and clinical laboratory evaluations were conducted.

Statistical analysis

Efficacy analyses were performed on all randomized patients who received at least 1 dose of the study drug, defined as the modified intent-to-treat (mITT) population. All patients received their treatment of assignment; consequently, the mITT population in this study was identical to the safety-evaluable population used for the safety analyses.

Poisson regression model adjusted for overdispersion was used to analyze the primary efficacy end point to assess the effect of omalizumab on the rate of protocol-defined asthma exacerbations. A nonparametric comparison between treatment groups was performed by using the rank-based van Elteren test with standardized midrank (modified ridit) weights.

Analysis of all primary and secondary efficacy end points was adjusted for 2 covariates: dosing schedule (every 2 or 4 weeks) and prior exacerbation status. The common RR was estimated across strata, and the corresponding 95% CI was calculated.

Percentage predicted FEV_1 values were calculated on the basis of the method of Crapo et al[E3] for patients 18 years or older and the method of Polgar and Promadhat[E4] for patients younger than 18 years. Absolute change from baseline to week 24 was compared between treatment groups by using an analysis of covariance (ANCOVA) model in which the baseline % predicted FEV_1 value, dosing regimen, and asthma exacerbation status (during the 12 months prior to screening or during the run-in period) were covariates. Relative change from baseline to week 24 was compared between treatment groups by using an ANOVA model. The last-observation-carried-foward (LOCF) method was used for imputation of missing data for patients who discontinued prematurely.

Change from baseline to week 24 in nocturnal and daytime asthma symptom scores was compared between treatment groups by using an ANCOVA model with covariates including baseline symptom scores, dosing regimen, and asthma exacerbation status. When symptom scores were unavailable for more than 7 days out of the 28 days prior to a given visit, the mean symptom scores were considered missing for the visit and were imputed by using the LOCF method.

In the context of multiple hypothesis testing, the familywise type I error was controlled through a gatekeeping strategy with the end points in the following statistical hierarchy: the primary end point of average rate of protocol-defined asthma exacerbations during the 24-week treatment period, followed, in order, by the secondary end points of changes at week 24 from baseline in % predicted FEV_1, changes in nocturnal symptoms score, and changes in daytime symptoms score. If a lack of statistical significance was identified at any level, then testing could not continue beyond that level.

A preplanned subgroup analysis was conducted to evaluate the effect on eosinophil counts at screening, with patients divided into 2 groups: low (<300/μL) and high (≥300/μL). This analysis was planned prior to unblinding of the study data in response to accumulating evidence about the importance of eosinophil counts in atopic asthma. However, eosinophil counts were not necessarily collected for all patients at baseline and may therefore have been missing at random depending on their availability in the original laboratory test records. Preplanned subgroup analyses were also conducted to evaluate the effect of study drug dosing regimen (2 weeks vs 4 weeks) and prior exacerbation status (yes/no; during the 12 months prior to screening or during the run-in period).

As this study was designed to fulfill a postmarketing commitment to study omalizumab in a population that was not consistent with that for which treatment is indicated in clinical practice, the number of patients eligible for enrollment was highly limited. According to current Global Initiative for

Asthma (GINA) guidelines on asthma management, omalizumab is recommended as an add-on treatment to a medium- or high-dose ICS plus long-acting β_2-agonist following failure of a leukotriene modifier or sustained-release theophylline.[E5] At the end of the 4-year recruiting period, approximately 330 patients had been enrolled. Under a Poisson regression model, 330 patients provided approximately only 30% power to demonstrate a statistically significant treatment effect for the 27% reduction in the asthma exacerbation rate observed in this study.

RESULTS

The study was conducted at 81 centers in the United States, and patient disposition is shown in Fig E1. The study was completed by 289 (86.8%) patients (84.9% of the omalizumab group; 88.5% of the placebo group). Overall, 328 patients received at least 1 dose of study treatment (mITT population); 2 patients in the omalizumab group and 3 in the placebo group were randomized but did not receive treatment as they were found to be ineligible after randomization.

Patient demographics and baseline characteristics were well balanced between the treatment groups (Tables E1 and E2). The majority of patients (79.3%) received concomitant ICS and long-acting β_2-agonist, which included 4.9% receiving a third controller. During the 12 months prior to randomization and during the run-in period, 38.7% of the patients had no exacerbations, 48.8% had 1 asthma exacerbation, and 12.5% had 2 or more exacerbations.

Secondary efficacy analyses

One omalizumab-treated patient had a low baseline FEV_1 value of 0.95 L, resulting in relative changes of more than 200% in FEV_1 at subsequent visits. The spirometry data from this patient were considered outliers, and were removed from the analysis. Mean ± SD FEV_1 increased by 0.055 ± 0.319 L from baseline to week 24 in the omalizumab group, compared with a decrease of 0.026 ± 0.338 L in the placebo group. Mean ± SD % predicted FEV_1 increased by 1.78 ± 9.69 in the omalizumab group and decreased by 0.98 ± 10.2 in the placebo group. Based on the ANOVA model, the treatment effect in relative change of FEV_1 was estimated to be 3.5% (95% CI, 0.9-6.1) (Fig E2).

Change in mean ± SD nocturnal asthma symptom scores at week 24 from baseline was summarized as −0.48 ± 0.77 in the omalizumab group and −0.49 ± 0.67 in the placebo group. Change in mean ± SD daytime asthma symptom scores was summarized as −0.73 ± 0.72 in the omalizumab group and −0.67 ± 0.72 in the placebo group. Based on the ANCOVA model, the treatment effects in change in nocturnal and daytime asthma symptom scores were not statistically significant and estimated to be 0.01 (95% CI, −0.12 to 0.14) and −0.05 (95% CI, −0.19 to 0.09), respectively.

Subgroup analyses

Data on the peripheral blood eosinophil counts at screening were retrieved from 217 of 328 patients in the mITT population in support of a prespecified analysis. Of note, 91 (41.9%) patients had an eosinophil count of 300/μL or more at baseline.

In patients with a high eosinophil count at baseline, the least squares mean treatment effect for relative change in FEV_1 from baseline to week 24 was estimated to be 7.35% (95% CI, 1.38-13.31). In patients with a low baseline eosinophil count, the least squares mean treatment effect for relative change in FEV_1 was 3.67% (95% CI, −0.46 to 7. 81).

There were no significant differences in treatment effect between treatment groups when patient data were analyzed according to exacerbation history or dosing regimen (Fig E3). Notably, in patients with and without a exacerbation history, protocol-defined exacerbation rates per patient were 0.30 and 0.04 in the omalizumab group and 0.40 and 0.06 in the placebo group, respectively, during the 24-week treatment period. Indeed, this subgroup analysis demonstrated that there was no information contributed by patients with no prior exacerbations (Table E3).

No correlation was found between baseline IgE levels and eosinophil counts at screening (data not shown).

Sensitivity analyses

Exacerbations according to the ATS definition. The ATS definition specifies that in clinical trials a severe asthma exacerbation should include at least 1 of the following: (1) use of systemic corticosteroids or an increase from a stable maintenance dose, for at least 3 days; or (2) hospitalization or emergency room visit because of asthma, and requiring systemic corticosteroids. Moderate exacerbations are defined as events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation.[E6]

Sensitivity analyses were conducted to explore the effect of omalizumab on exacerbations defined according to these ATS definitions (ie, excluding doubling of ICS from the definition).

FEV_1 data. For the total study population, including a patient with outlying values, mean percentage predicted FEV_1 increased by 3.8% in the omalizumab group and decreased by 1.0% in the placebo group from baseline to week 24. Mean FEV_1 increased by 0.064 L from baseline to week 24 in the omalizumab group, compared with a decrease of 0.027 L in the placebo group. Based on the ANOVA model, the treatment effect in relative change from baseline in FEV_1 at week 24 was estimated to be 4.8% (95% CI, 1.2-8.4) (Fig E4).

Safety

The overall incidence of AEs reported with omalizumab was similar to that of the placebo group; most AEs were mild or moderate in severity, and serious AEs were uncommon (Table E4). Four patients (1.2%) discontinued the study because of an AE: 3 patients in the omalizumab group and 1 patient in the placebo group. In the omalizumab group, 1 patient each reported a serious AE (arterial thromboembolic event and breast cancer), neither of which was considered to be related to the study drug; 1 patient reported AEs of pollakiuria and micturition urgency that were considered to be related to the study drug. The patient in the placebo group reported a serious AE of diffuse large B-cell lymphoma. No deaths were observed during the treatment or follow-up periods.

No clinically relevant laboratory findings, including platelet count results, were reported. The incidence of treatment-emergent AEs of special interest (malignancies, urticaria, hypersensitivity reaction, injection-site reaction, bleeding-related events, and arterial thromboembolic event) was low and similar between treatment groups. No AEs qualified as anaphylaxis, serum sickness syndrome, Churg-Strauss syndrome, or parasitic infections.

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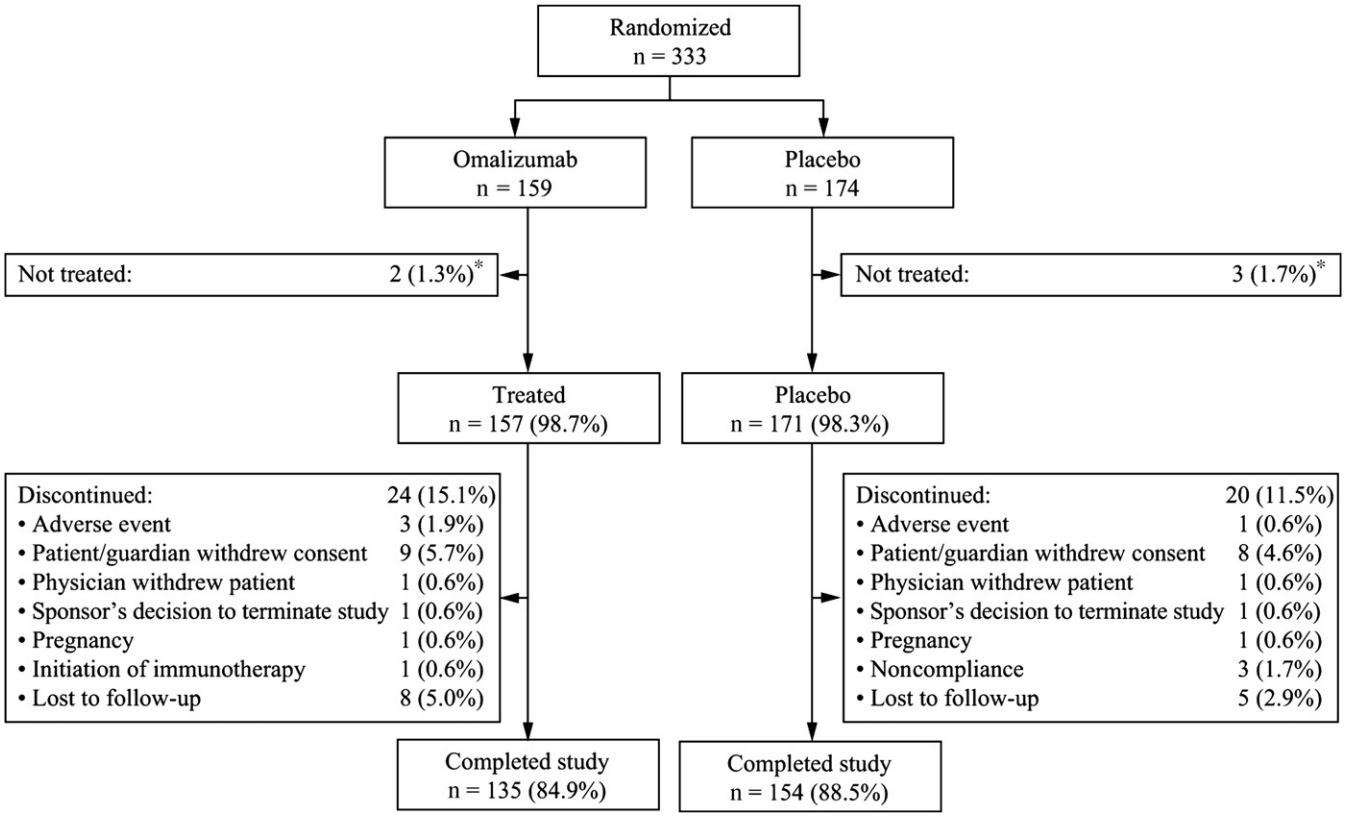

FIG E1. Patient disposition. *Five patients were found to be ineligible after enrollment.

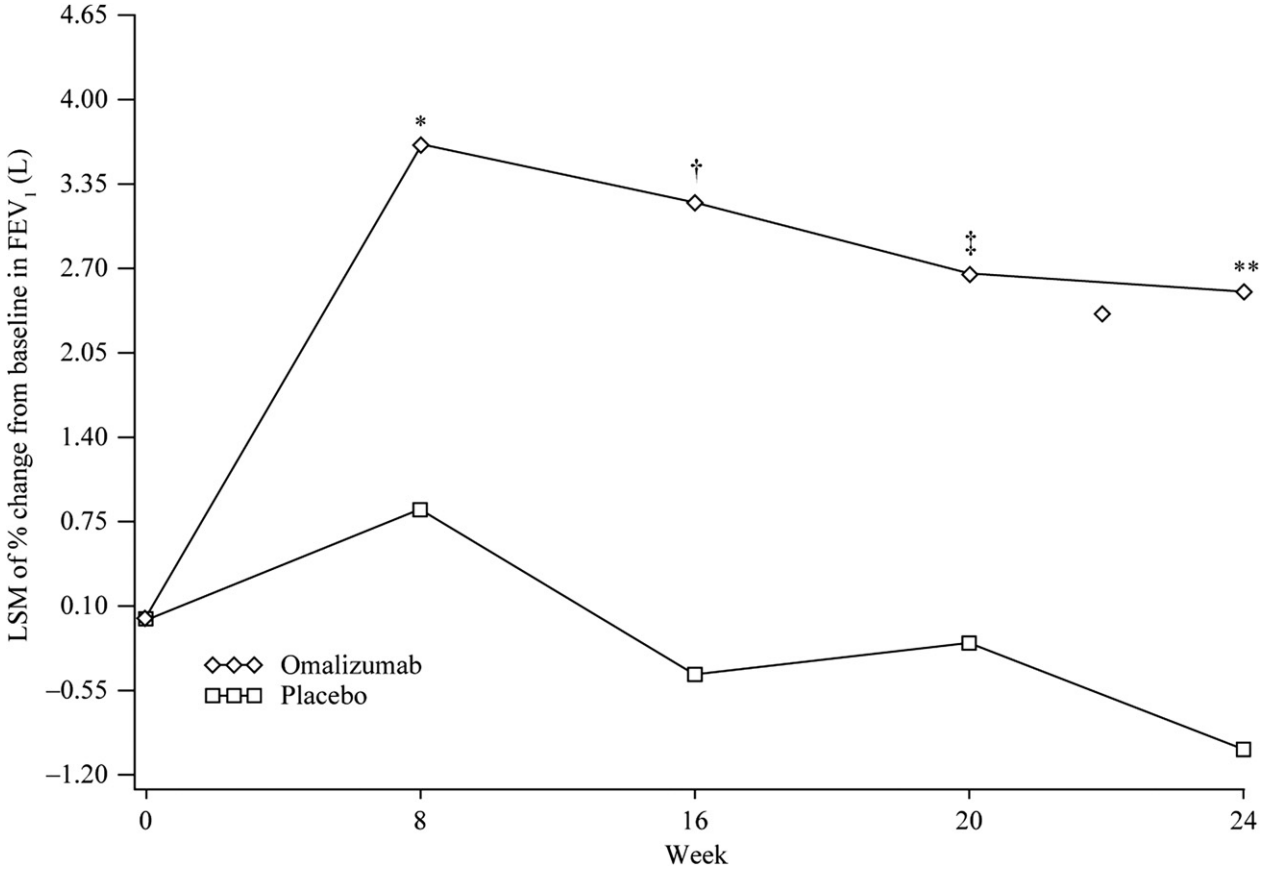

FIG E2. Least squares means of relative change from baseline in FEV_1 (mITT population [excluding 1 patient with outlying spirometry data]). *LSM,* Least squares means (adjusted for dosing regimen and prior exacerbation status). *$P = .04$; †$P = .002$; ‡$P = .02$; **$P = .008$.

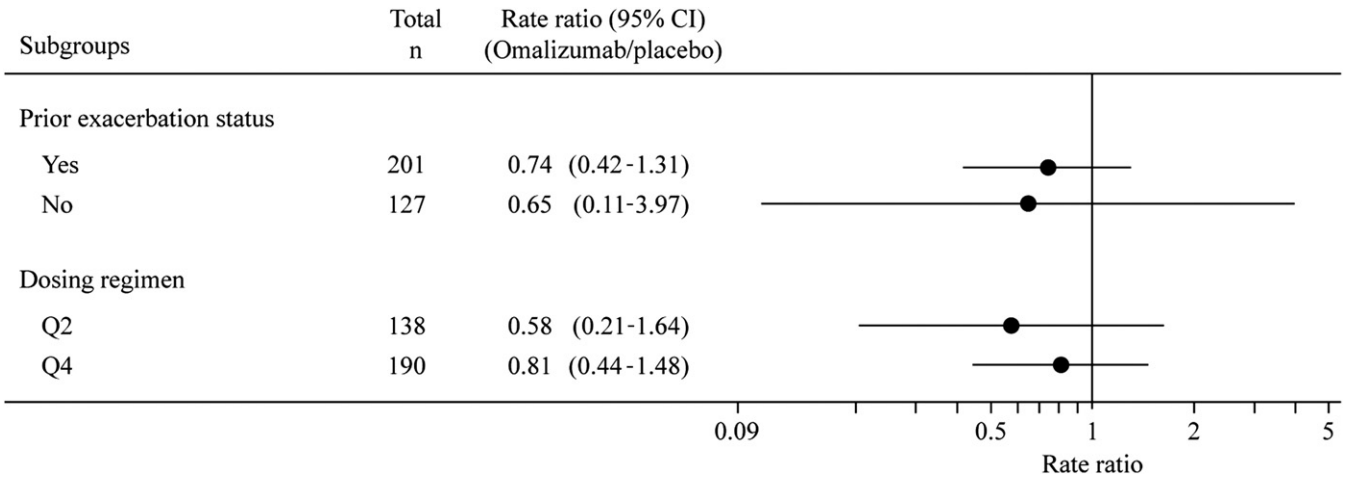

FIG E3. Rate ratio (95% CI) of protocol-defined asthma exacerbation by prior exacerbation status and dosing regimen subgroups. Q2, every 2 wk; Q4, every 4 wk.

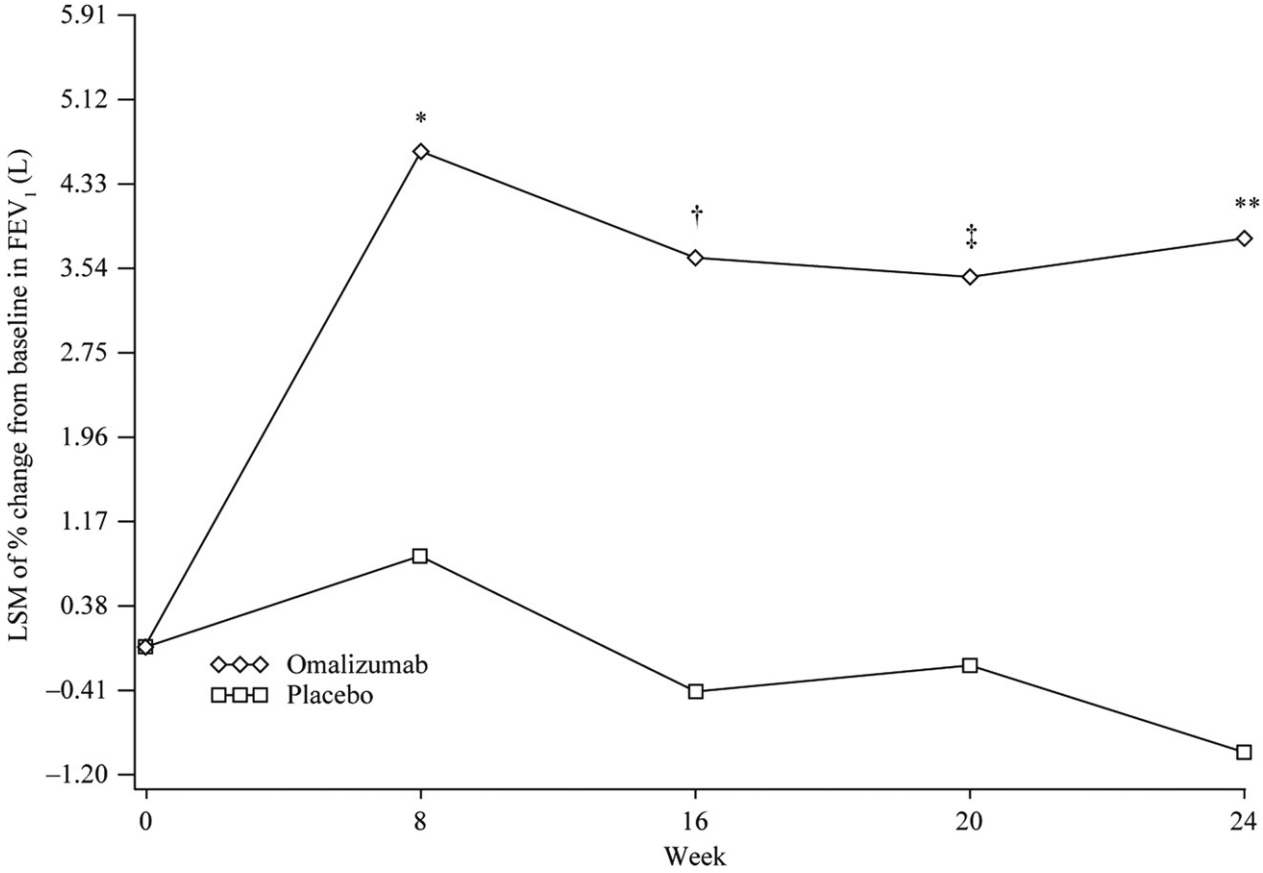

FIG E4. Least squares means of relative change from baseline in FEV_1 (mITT population). *LSM*, Least squares means (adjusted for dosing regimen and prior exacerbation status). $*P = .02$; $\dagger P = .001$; $\ddagger P = .01$; $**P = .009$.

TABLE E1. Patient demographics and baseline characteristics (mITT population)

	Omalizumab (n = 157)	Placebo (n = 171)
Age (y), n (%)		
12-17	25 (25.9)	20 (11.7)
18-64	127 (80.9)	143 (83.6)
≥65	5 (3.2)	8 (4.7)
Age, mean ± SD (y)	36.0 ± 14.7	38.1 ± 15.1
Sex, n (%)		
Male	47 (29.9)	55 (32.2)
Female	110 (70.1)	116 (67.8)
Race, n (%)		
White	113 (72)	118 (69)
Black or African American	37 (23.6)	42 (24.6)
Asian	5 (3.2)	4 (2.3)
American Indian/Alaska Native	1 (0.6)	3 (1.8)
Other	1 (0.6)	4 (2.3)
Body weight (kg), mean ± SD	77.9 ± 21.6	83.2 ± 21.9
Total serum IgE (IU/mL), mean ± SD	196.3 ± 160.2	199.7 ± 168.3*
Prebronchodilator FEV_1 (L), mean ± SD	2.8 ± 0.7	2.8 ± 0.7
Prebronchodilator FEV_1 (% predicted), mean ± SD	85.7 ± 13.4	85.9 ± 11.4*
Prior exacerbations†		
0	58 (36.9)	69 (40.4)
1	80 (51.0)	80 (46.8)
2	13 (8.3)	19 (11.1)
≥3	6 (3.8)	3 (1.8)
Concomitant asthma medications, n (%)		
ICS alone	30 (19.1)	33 (19.3)
ICS + LABA‡	124 (79.0)	136 (79.5)
ICS + LABA + other controllers‡	7 (4.5)	9 (5.3)
ICS dose (μg), mean ± SD	488.7 ± 258.8	527.7 ± 271.1*
Puffs of rescue medication, mean ± SD		
Morning	1.2 ± 1.0	1.2 ± 1.1*
Evening	1.6 ± 1.2	1.7 ± 1.5§
Asthma symptom score, mean ± SD		
Nocturnal	1.1 ± 0.9	1.0 ± 0.8*
Daytime	1.5 ± 0.7	1.5 ± 0.7*
Eosinophil counts (L)		
<300/μL	56 (52.3)‖	70 (63.6)¶
≥300/μL	51 (47.7)‖	40 (36.4)¶

LABA, Long-acting β_2-agonist.
*n = 170.
†Exacerbations during the 12 mo prior to screening and during the run-in period.
‡The category "ICS + LABA" includes patients in the category "ICS + LABA + other controllers."
§n = 169.
‖n = 107.
¶n = 110.

TABLE E2. Patient demographics and baseline characteristics for the subgroups of patients with high or low eosinophil counts

	High eosinophil subgroup (≥300/L)		Low eosinophil subgroup (<300/L)	
	Omalizumab (n = 51)	Placebo (n = 40)	Omalizumab (n = 56)	Placebo (n = 76)
Age (y), n (%)				
12-17	11 (21.6)	7 (17.5)	7 (12.5)	7 (10.0)
18-64	38 (74.5)	32 (80.0)	48 (85.7)	61 (87.1)
≥65	2 (3.9)	1 (2.5)	1 (1.8)	2 (2.9)
Age (y), mean ± SD	34.2 ± 15.8	35.2 ± 15.4	36.1 ± 13.1	38.1 ± 14.5
Sex, n (%)				
Male	18 (35.3)	9 (22.5)	12 (21.4)	25 (35.7)
Female	33 (64.7)	31 (77.5)	44 (78.6)	45 (64.3)
Race, n (%)				
White	41 (8.04)	28 (70.0)	39 (69.6)	50 (71.4)
Black or African American	7 (13.7)	8 (20.0)	14 (25.0)	16 (22.9)
Asian	2 (3.9)	2 (5.0)	3 (5.4)	2 (2.9)
American Indian/Alaska Native	0	1 (2.5)	0	0
Other	1 (2.0)	1 (2.5)	0	2 (2.9)
Body weight (kg), mean ± SD	79.0 ± 19.0	81.8 ± 23.7	75.7 ± 20.1	85.9 ± 22.8
Total serum IgE (IU/mL), mean ± SD	184.8 ± 117.2	239.6 ± 158.7*	176.1 ± 147.8	149.9 ± 136.6
Prebronchodilator FEV_1 (L), mean ± SD	2.8 ± 0.8	2.7 ± 0.6	2.7 ± 0.5	2.9 ± 0.7
Prebronchodilator FEV_1 (% predicted), mean ± SD	83.9 ± 12.3	83.5 ± 11.0	86.6 ± 11.9	86.3 ± 11.1
Prior exacerbations†				
0	14 (27.5)	9 (22.5)	20 (35.7)	28 (40.0)
1	28 (54.9)	24 (60.0)	31 (55.4)	33 (47.1)
2	8 (15.7)	6 (15.0)	1 (1.8)	9 (12.9)
≥3	1 (2.0)	1 (2.5)	4 (7.1)	0
Concomitant asthma medications, n (%)				
ICS alone	10 (19.6)	8 (20.0)	14 (25.0)	13 (18.6)
ICS + LABA‡	40 (78.4)	32 (80.0)	41 (73.2)	57 (81.4)
ICS + LABA + other controllers‡	5 (9.8)	1 (2.5)	1 (1.8)	6 (8.6)
ICS dose (μg), mean ± SD	516.1 ± 262.8	528.5 ± 283.1	492.8 ± 307.4	568.4 ± 283.0
Puffs of rescue medication, mean ± SD				
Morning	1.3 ± 1.2	1.2 ± 1.1	1.2 ± 1.0	1.2 ± 1.1
Evening	1.8 ± 1.2	1.7 ± 1.8	1.5 ± 1.3	1.7 ± 1.2
Asthma symptom score, mean ± SD				
Nocturnal	0.9 ± 0.9	1.1 ± 0.8	1.0 ± 0.8	1.0 ± 0.8
Daytime	1.6 ± 0.6	1.5 ± 0.9	1.5 ± 0.7	1.5 ± 0.6

LABA, Long-acting β_2-agonist.

*n = 39.

†Exacerbations during the 12 mo prior to screening and during the run-in period.

‡The category "ICS + LABA" includes patients in the category "ICS + LABA + other controllers."

TABLE E3. Change in protocol-defined asthma exacerbation rate over the 24-week treatment period by status of having prior exacerbations (mITT population)

Having prior exacerbations	Omalizumab	Placebo
Yes	n = 99	n = 102
No. of protocol-defined asthma exacerbations, n (%)		
0	77 (77.8)	73 (71.6)
1	19 (19.2)	21 (20.6)
≥2	3 (3.0)	8 (7.8)
Unadjusted exacerbation rate*	0.30	0.40
Poisson regression†		
Ratio of exacerbation rates‡ (95% CI)	0.74 (0.42-1.31)	
P value	.3026	
No	n = 58	n = 69
No. of protocol-defined asthma exacerbations, n (%)		
0	56 (96.6)	65 (94.2)
1	2 (3.4)	4 (5.8)
≥2	0 (0.0)	0 (0.0)
Unadjusted exacerbation rate*	0.04	0.06
Poisson regression†		
Ratio of exacerbation rates‡ (95% CI)	0.65 (0.11-3.97)	
P value	.6407	

*Number of protocol-defined asthma exacerbations/total patient-treatment period.
†Poisson regression with overdispersion model is adjusted for dosing regimen.
‡Omalizumab/placebo.

TABLE E4. Number (%) of patients with AEs (safety-evaluable population)

	Omalizumab (n = 157)	Placebo (n = 171)
Any AE	92 (58.6)	108 (63.2)
Serious AE	4 (2.5)	6 (3.5)
AEs with incidence >3% in any treatment group*		
Upper respiratory tract infection	15 (9.6)	17 (9.9)
Sinusitis	11 (7.0)	16 (9.4)
Nasopharyngitis	9 (5.7)	16 (9.4)
Influenza	7 (4.5)	1 (0.6)
Headache	7 (4.5)	10 (5.8)
Cough	7 (4.5)	5 (2.9)
Asthma	5 (3.2)	5 (2.9)
Pharyngitis	4 (2.5)	6 (3.5)
Back pain	3 (1.9)	6 (3.5)
Allergic rhinitis	3 (1.9)	7 (4.1)
Arthralgia	2 (1.3)	6 (3.5)
AEs of special interest		
Malignancies	1 (0.6)	1 (0.6)
Urticaria	3 (1.9)	3 (1.8)
Hypersensitivity reaction	2 (1.3)	4 (2.3)
Injection-site reaction	2 (1.3)	1 (0.6)
Bleeding-related events	4 (2.5)	3 (1.8)
Arterial thromboembolic event	1 (0.6)	0

*MedDRA system organ class preferred term; ranked by frequency in the omalizumab group.